Clinical Relevance for the Veteran

From the bench to the body: Key issues associated with research aimed at a cure for SCI

Marca L. Sipski, MD

Purpose of the Work. Every day, researchers make progress toward a cure for spinal cord injury (SCI). However, a significant number of issues still need to be addressed in order to translate new findings in laboratory animals to general clinical use for humans. **Relevance to the Veteran Population.** The goal of this article is to highlight these issues so that clinicians will understand them and be more adept at counseling their patients about this important topic.

Marca L. Sipski, MD

Brain-dependent movements and cerebral-spinal connections: Key targets of cellular and behavioral enrichment in CNS injury models

Timothy Schallert, PhD; Martin T. Woodlee, BS

Purpose of the Work. In this article, we describe the effects of early behavioral rehabilitation in animal models of human spinal cord injury, Parkinson's disease, and stroke. We also critically review recent studies of neural and glial events linked to motor enrichment interventions and argue that an assessment of voluntary motor capacity should be included in preclinical research. Also given are some potential pitfalls of translating the results of rodent studies into clinical trials. **Relevance to the Veteran Population.** This article should be of interest to neurologists, physical therapists, and other clinicians who treat patients.

Timothy Schallert, PhD

Quantification of functional behavior in humans and animals: Time for a paradigm shift

Edelle Carmen Field-Fote, PhD, PT

Purpose of the Work. This article advocates the use of quantitative methods for the analysis of movement. **Procedures.** Descriptions and examples of various forms of kinematic analysis are reviewed and their applications discussed. **Results.** Kinematic analysis allows for definitive comparisons of motor performance. This facilitates an understanding of how movement changes within an animal or individual as a result of treatment. It is also useful for analyzing how movement differs between groups of animals or individuals that have undergone different interventions. **Relevance to the Veteran Population.** Quantitative analysis of movement is essential to understanding what treatments yield the best results in terms of motor function. Kinematic analysis is valuable in both research and clinical applications.

Edelle Carmen Field-Fote, PhD, PT

Physiological methods to measure motor function in humans and animals with spinal cord injury

Christine K. Thomas, PhD; Brian R. Noga, PhD

Purpose of the Work. This article compares physiological methods that are commonly used to measure the functional capability of the motor system in humans and animals after spinal cord injury. **Procedures**. Literature involving humans and animals with and without spinal cord injury is reviewed. **Results**. The experimental methods and conditions that are used to evaluate motor function in humans and animals can differ. Despite this, there are ways to measure the effectiveness of conduction through the motor system, to assess coordination of different inputs at the spinal cord, and to evaluate the responsiveness of the neuromuscular system. **Relevance to the Veteran Population**. Comparisons across species are invaluable to understand the control of movement both before and after spinal cord injury. These data are particularly useful in the design of clinical trials that involve individuals with spinal cord injury, including veterans.

Christine K. Thomas, PhD

Methods to measure sensory function in humans versus animals

Alberto Martinez-Arizala, MD

Purpose of the Work. The purpose of this article is to review the current state of the art of sensory testing in the field of spinal cord injury (SCI). **Relevance to the Veteran Population.** This information is relevant to the veteran because it summarizes the present problems in the field of sensation testing in SCI and makes some future recommendations to improve this testing. Improvements in our tests will improve our ability to better assess the

recovery of sensory function following SCI and the effectiveness of new therapies.

Alberto Martinez-Arizala, MD

Common animal models for spasticity and pain

Mary Eaton, PhD

Purpose of the Work. This article is the textual representation of a platform session, "Common Animal Models of Pain and Spasticity," presented at the American Spinal Injury Association (ASIA) Pre-Course for the ASIA annual meeting, held 4–6 April 2003 in Miami, Florida. **Relevance to the Veteran Population.** Pain and spasticity are common sequelae of damage to the nervous system. This manuscript reviews the most commonly used animal models of pain and spasticity to illustrate how and where they are used to examine the mechanisms and treatments for these clinical problems.

Mary Eaton, PhD

Transplantation strategies to promote repair of the injured spinal cord

Mary Bartlett Bunge, PhD; Damien D. Pearse, PhD

Purpose of the Work. The purpose of this work is to create a milieu that will enable nerve fiber regeneration across the area of spinal cord injury and into the cord beyond to lead to an improvement in functional outcome. We have tried to conduct the experiments in as clinically relevant a way as possible. For example, we obtain Schwann cells from adult rats for our experiments because, if they are to be transplanted into a human, these cells would be obtained from an adult. **Relevance to the Veteran Population.** When we find a combination strategy that appears highly efficacious, then the experiment would be replicated in a chronic injury to eventually help those who have been in a wheelchair for some time.

Mary Bartlett Bunge, PhD

Confirming an experimental therapy prior to transfer to humans: What is the ideal?

W. Dalton Dietrich, PhD

Purpose of the Work. As the spinal cord injury (SCI) scientific community moves closer to translating experimental data to the clinic, specific steps require attention to improve our chances of success. Some of the steps under discussion include animal modeling, clinically relevant endpoints, compelling evidence for improvements, and safety issues. First, it will be beneficial if exciting data are first replicated before findings are considered clinically relevant. Then major findings must be published in peer-reviewed journals so that the scientific community may scrutinize the data. Finally, continued communication between different research groups throughout the world, as well as between basic scientists and clinicians working in the area of SCI, will enhance our progress in this important research field. **Relevance to the Veteran Population.** It is anticipated, once the data have been successfully replicated and the positive findings evaluated in clinical trials, that these results may improve the quality of life for individuals who are currently living with neurodegenerative disorders resulting from SCI.

W. Dalton Dietrich, PhD

Cellular therapies for spinal cord injury: What will the FDA need to approve moving from the laboratory to the human?

Jacqueline Sagen, PhD

Purpose of the Work. This article describes the process for advancing preclinical laboratory studies on cellular transplantation, particularly for spinal cord injury and pain, to initial clinical trials. **Subjects and Procedures.** A progression of work from preclinical rodent pain models to human subjects with intractable pain in phase I clinical trials. **Results.** The article explains the evolution of the regulatory processes and agencies overseeing initial clinical trials for cell and tissue transplantation. Important considerations for moving toward clinical trials are given. **Relevance to the Veteran Population.** As cell transplantation becomes better understood and novel methods are developed, it should be possible to improve clinical outcomes of devastating and currently incurable injuries and diseases. Injury to the nervous system, which can result in paralysis, chronic pain, and cognitive impairment, may be amenable to the cell-transplantation approaches. Thus, it is critical to gain an understanding of the regulatory process in order to expedite the implementation of these novel therapies.

Jacqueline Sagen, PhD

Drug development in spinal cord injury: What is the FDA looking for?

Edward D. Hall, PhD

Purpose of the Work. Much of the neurodegeneration and loss of function that follows acute spinal cord injury is due to a secondary cascade of pathochemical and pathophysiological events that exacerbate the damage caused by the primary mechanical injury. This process evolves rapidly during the first minutes and hours following injury, and a major player in the secondary injury is reactive oxygen-induced lipid peroxidation (LP). A high-dose regimen of the glucocorticoid steroid methylprednisolone (MP) has been shown to inhibit post-traumatic LP in animal models of SCI, and to improve neurological recovery in spinal cord-injured humans. This led to the registration of high-dose MP for acute SCI in several countries, although not in the U.S. Nevertheless, although it is controversial because of an uncertain risk-to-benefit ratio, this treatment quickly became, and remains in many centers, the standard of care for acute SCI since MP was already on the U.S. market for many other indications. Subsequently, the nonglucocorticoid 21-aminosteroid tirilazad was discovered, which was shown to duplicate the antioxidant neuroprotective efficacy of MP in SCI models, and evidence of human neuroprotective efficacy has been obtained with no evidence of glucocorticoid side effects. **Relevance to the Veteran Population.** This article explains the process of the discovery, development, and FDA regulation of new drugs for SCI; reviews the past development of MP and tirilazad; identifies the regulatory complications involved in future SCI drug development; and points out promising therapeutic approaches that could either replace or be added to high-dose MP.

Edward D. Hall, PhD

The consumer's perspective and the professional literature: What do persons with spinal cord injury want?

Irene M. Estores, MD

Purpose of the Work. This article summarizes the preferences and priorities of persons with spinal cord injury (SCI) as it relates to the motor, sensory, autonomic impairments arising from this injury and the consequent disability. **Procedures.** Articles from the National Library of Medicine (NLM) were reviewed and cited references were cross-referenced. **Results.** This review indicates that mobility remains the greatest concern, although pain, neurogenic bowel and bladder dysfunction, and physical and social changes related to aging are being reported as problems as well. Current SCI research addresses these issues. The methodology being used to ascertain the preferences of persons with SCI may need to be supplemented with different approaches. Longitudinal assessment of these preferences should be performed. **Relevance to the Veteran Population.** The information obtained regarding consumer preferences can serve as a framework for gathering relevant research from persons with spinal cord injury, which includes a significant number of veterans.

Irene M. Estores, MD